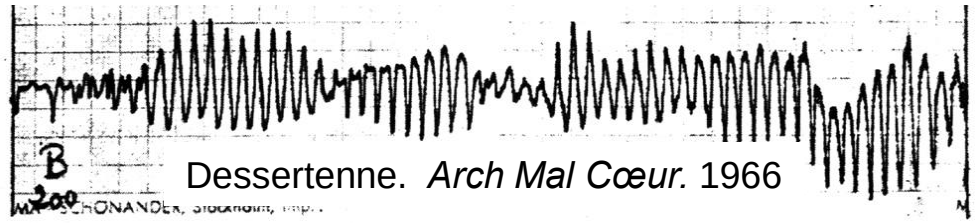
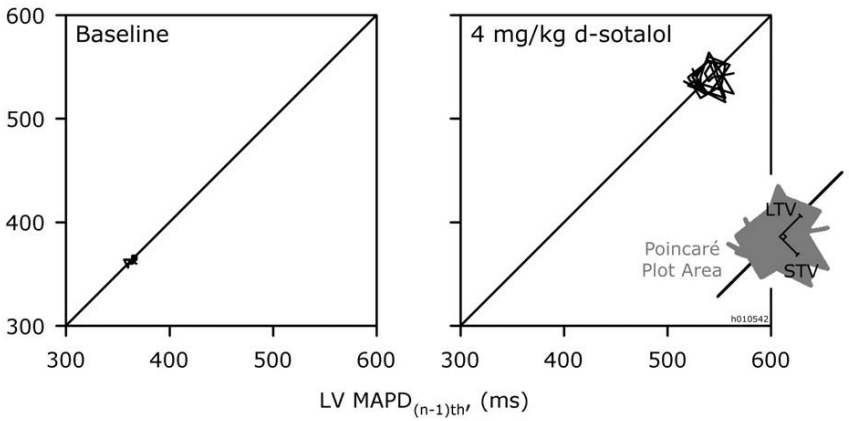
Diastolic Spontaneous Calcium Release from the Sarcoplasmic Reticulum Increases Beat-to-Beat Variability of Repolarization in Canine Ventricular Myocytes after β-Adrenergic Stimulation

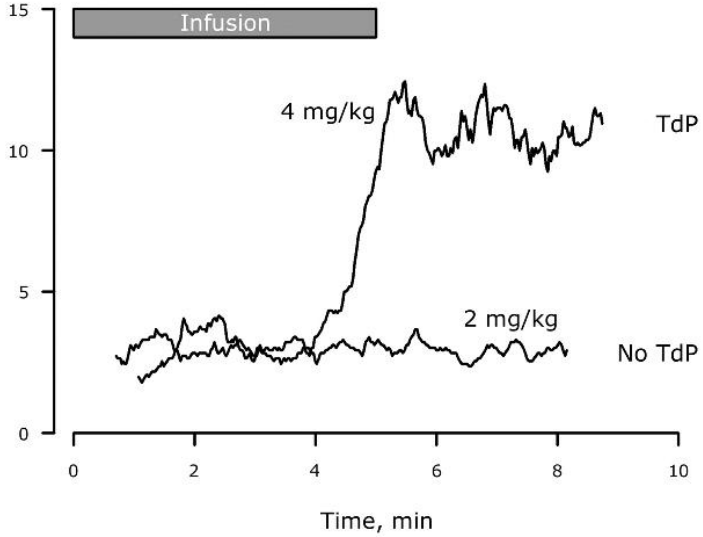


Dessertenne. *Arch Mal Cœur.* 1966

Dan Johnson
Department of Cardiology
Cardiovascular Research Institute, Maastricht

What is Beat-to-Beat Variability of Repolarization?

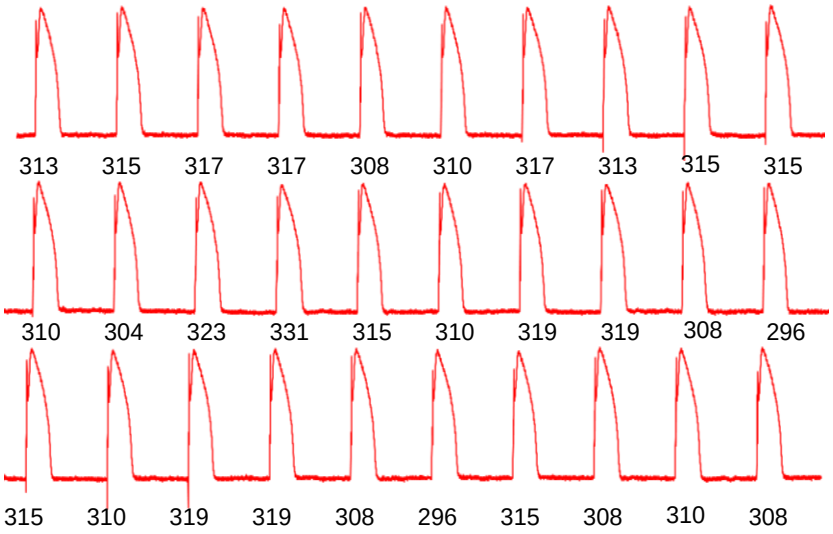




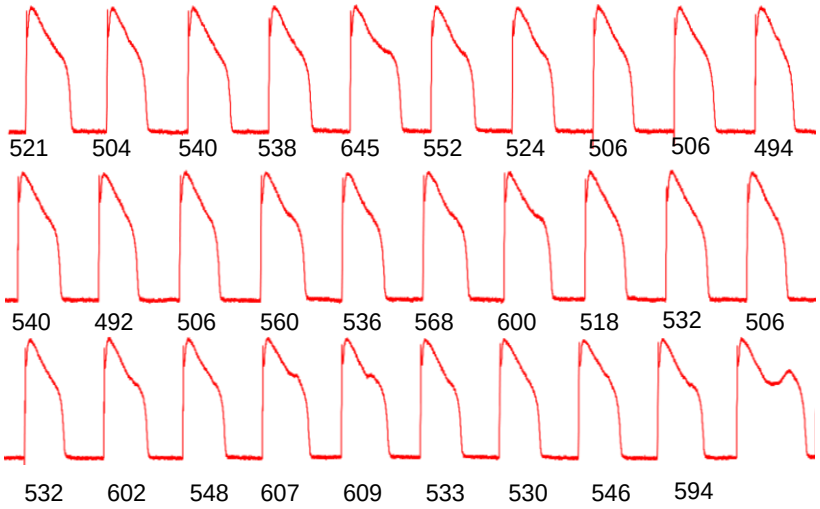
Thomsen et al; Circulation, 2004

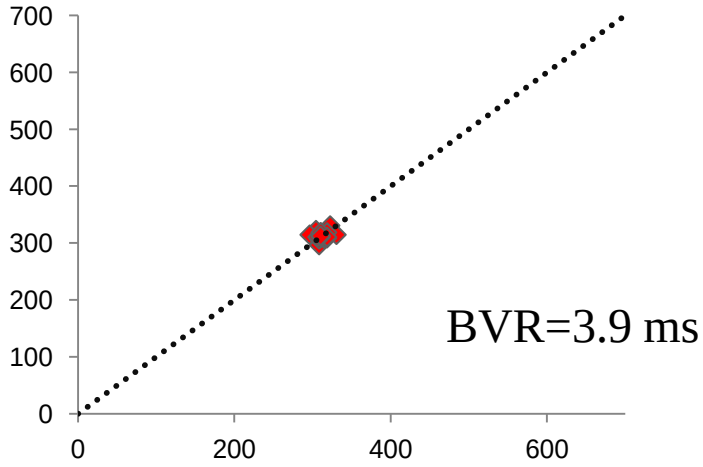
Cellular Beat-to-Beat Variability of Repolarization

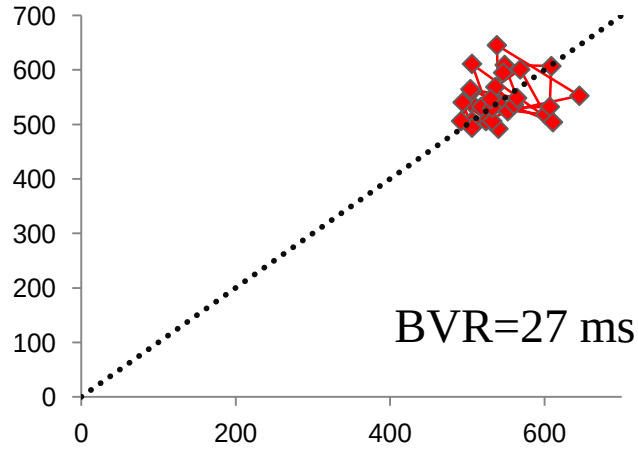
Baseline



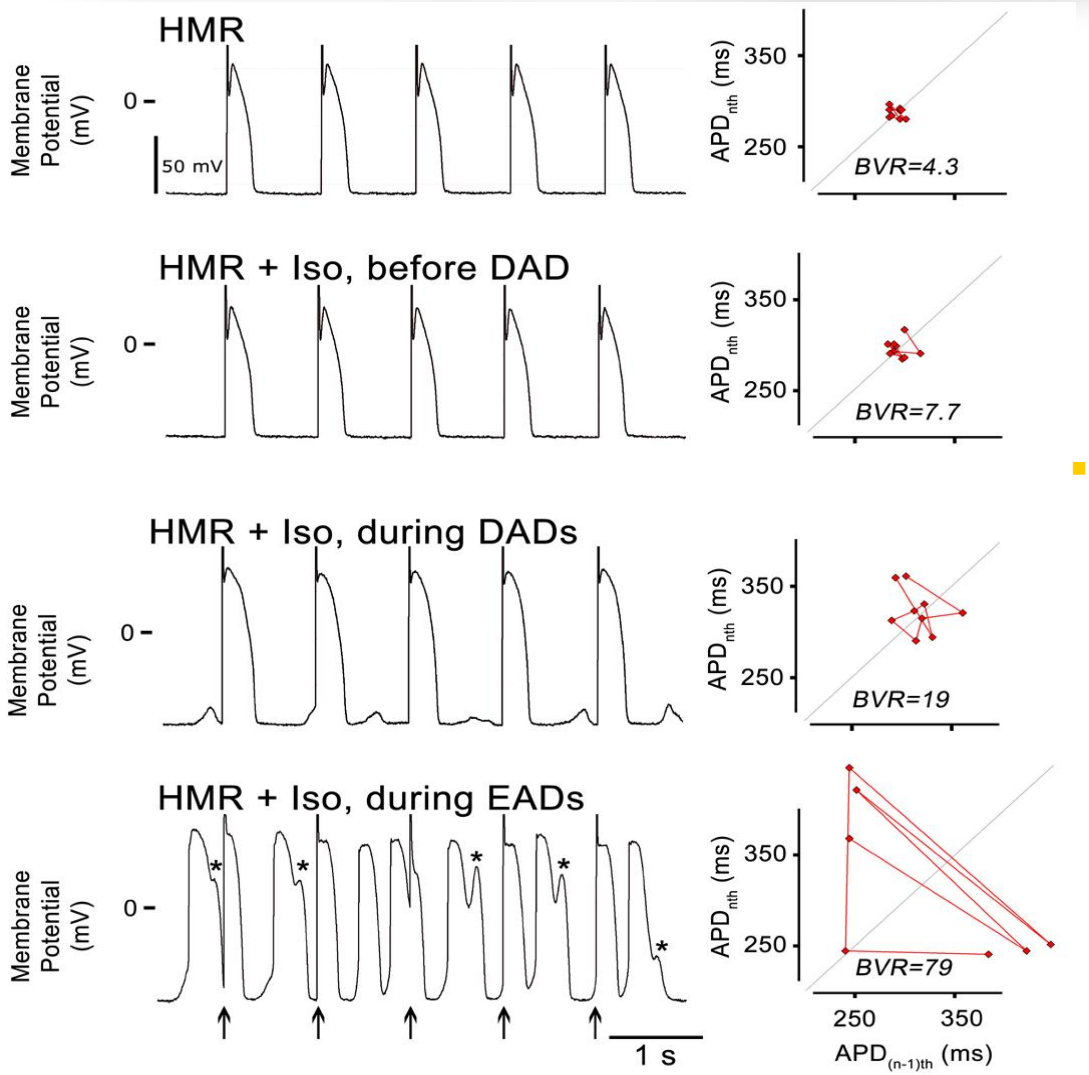
Proarrhythmic Conditions-ATX II







I_{Ks} and β-Adrenergic Stimulation



- Delayed after depolarizations profoundly influence BVR

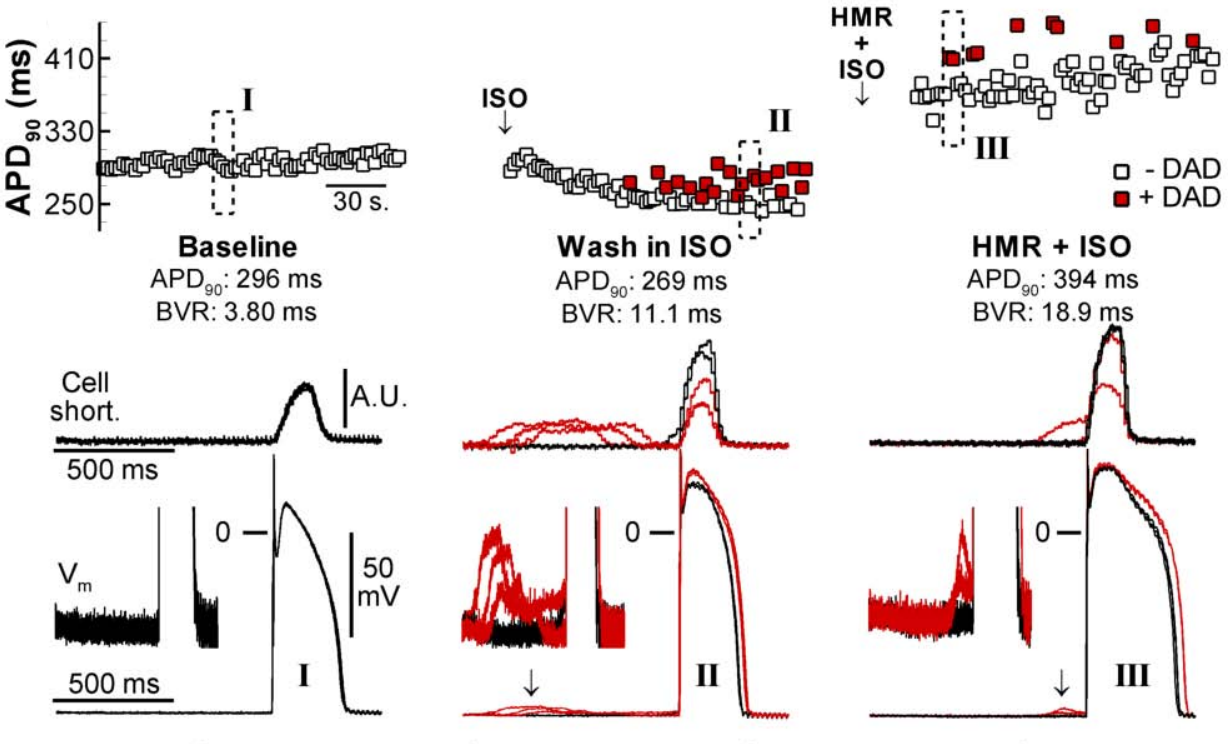
Johnson et al; JMCC 2010

Aims of present study

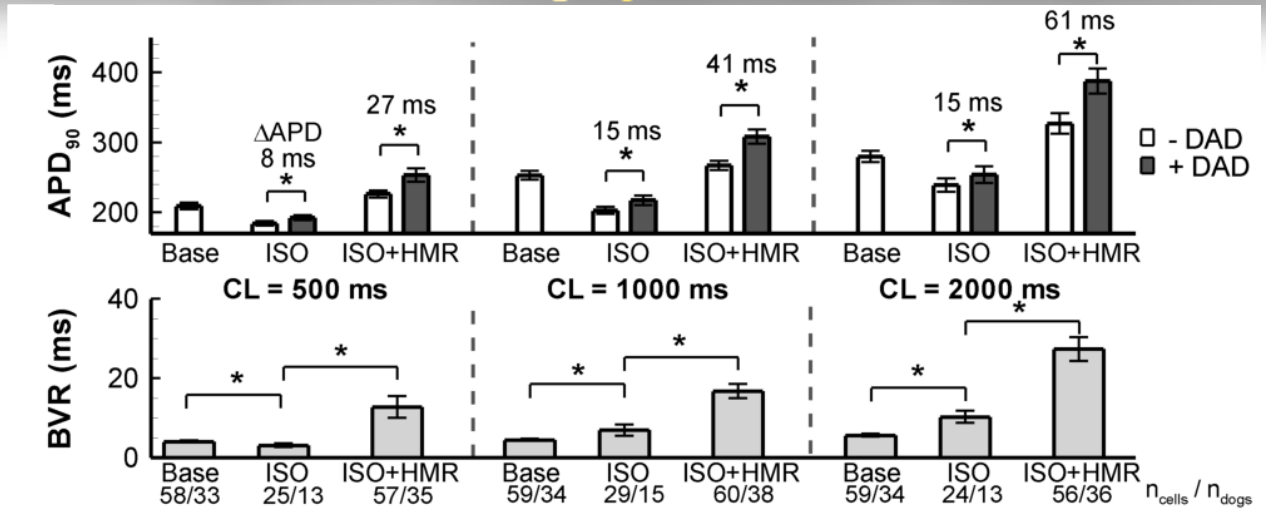
- **Aims-** To determine the ionic mechanisms that underlie increased BVR during calcium overload, such as that seen under LQT1 mimicking conditions, in the single canine ventricular myocyte

- **Hypothesis-** Diastolic spontaneous calcium release leads to interspersed action potential duration which will lead to increased BVR

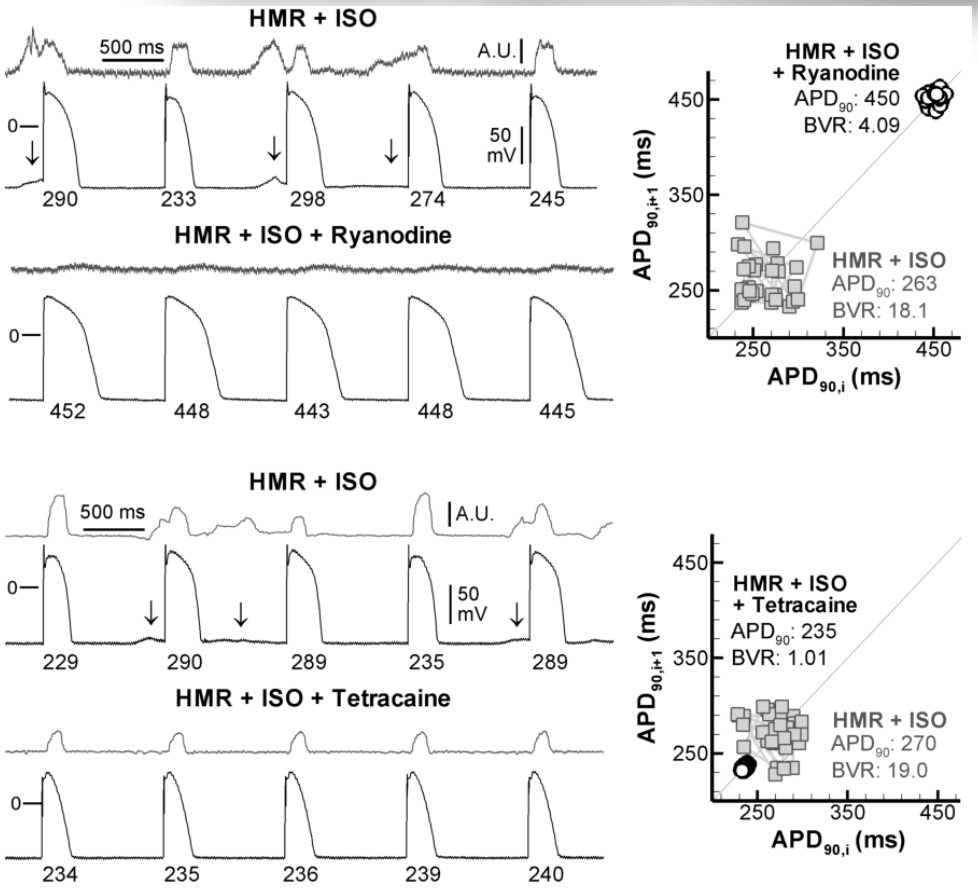
β-Adrenergic stimulation with and without IKs

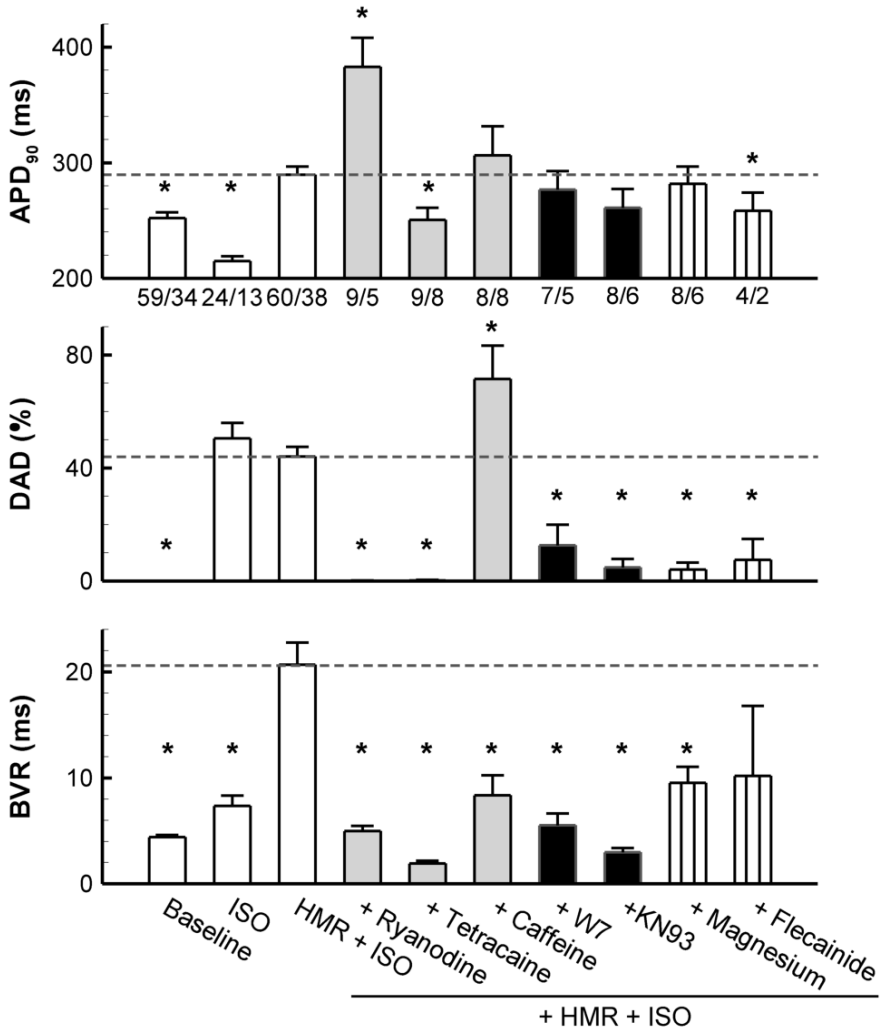


Cycle Length and Ca^{2+} Dependence

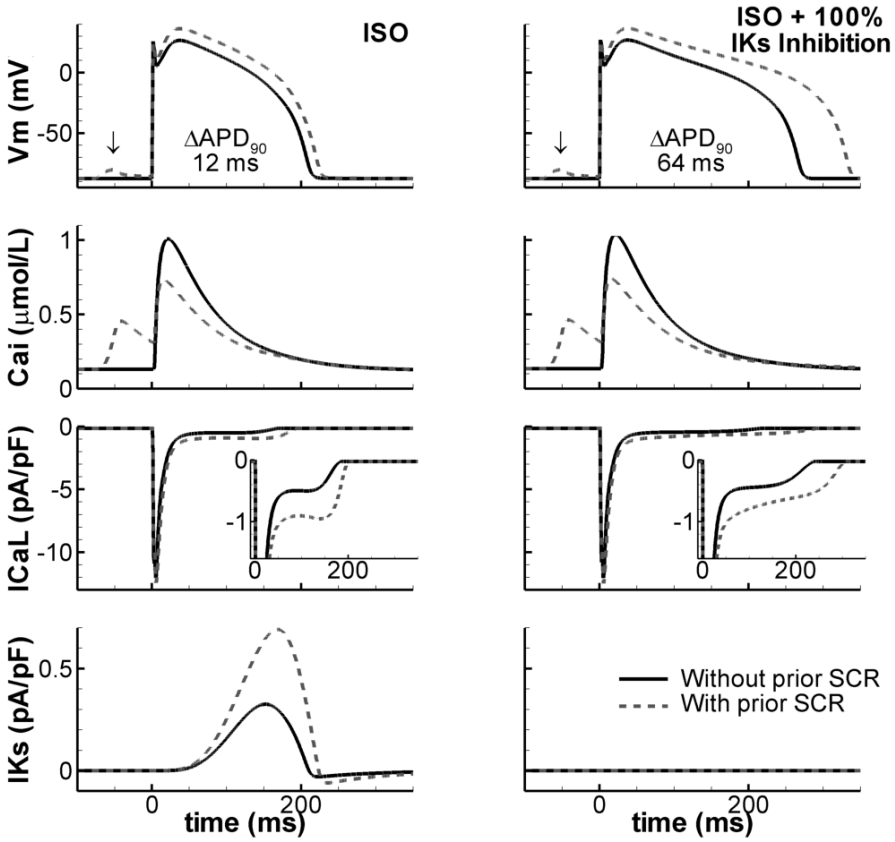


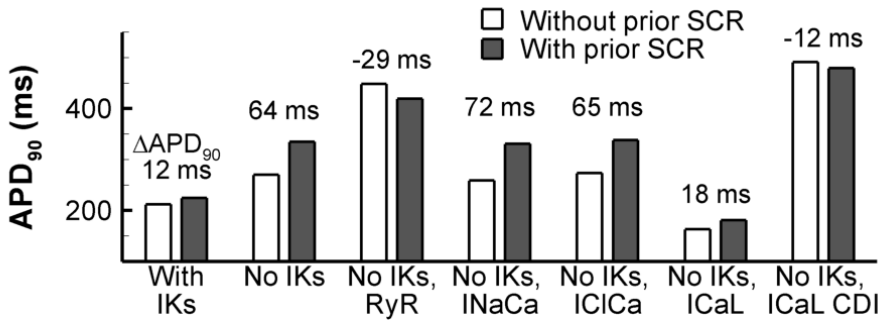
BVR Augmentation



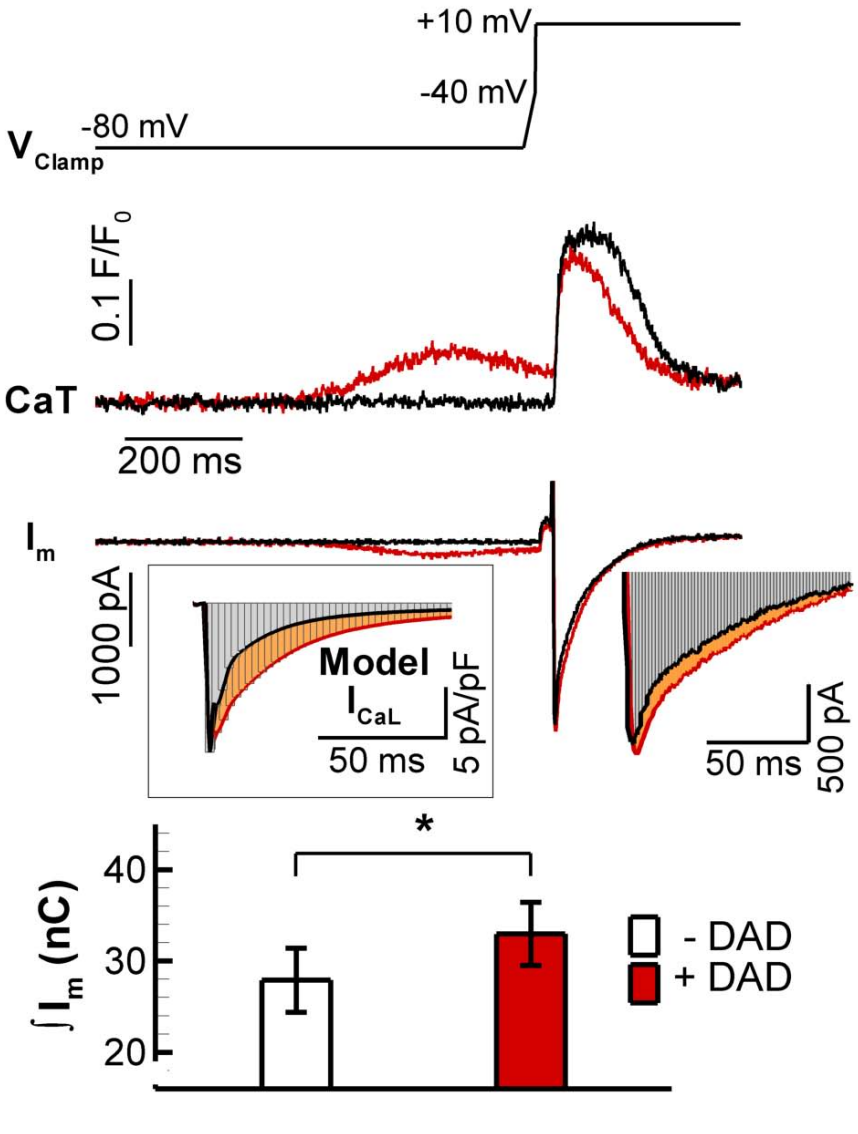


Underlying Mechanisms I

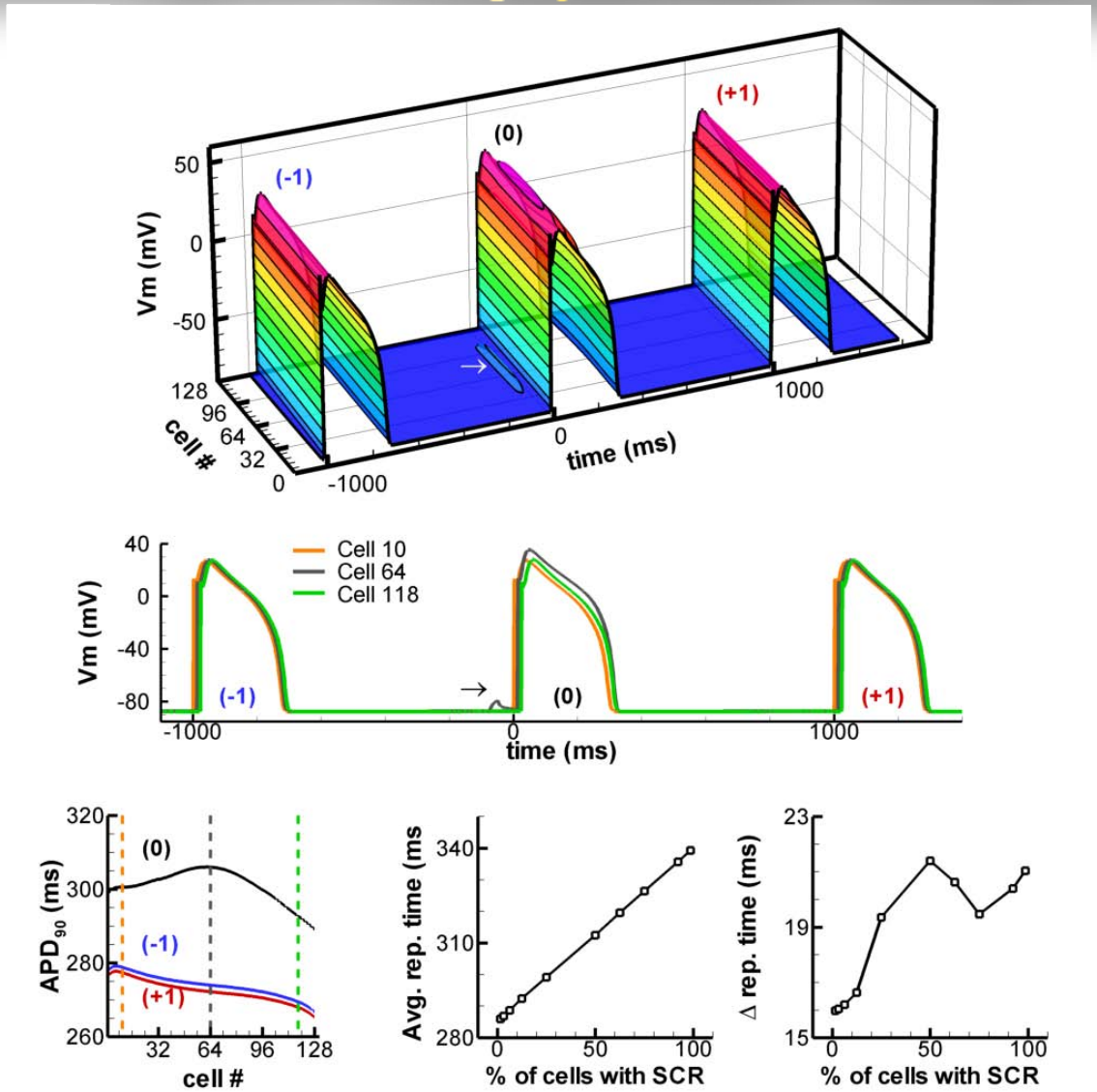




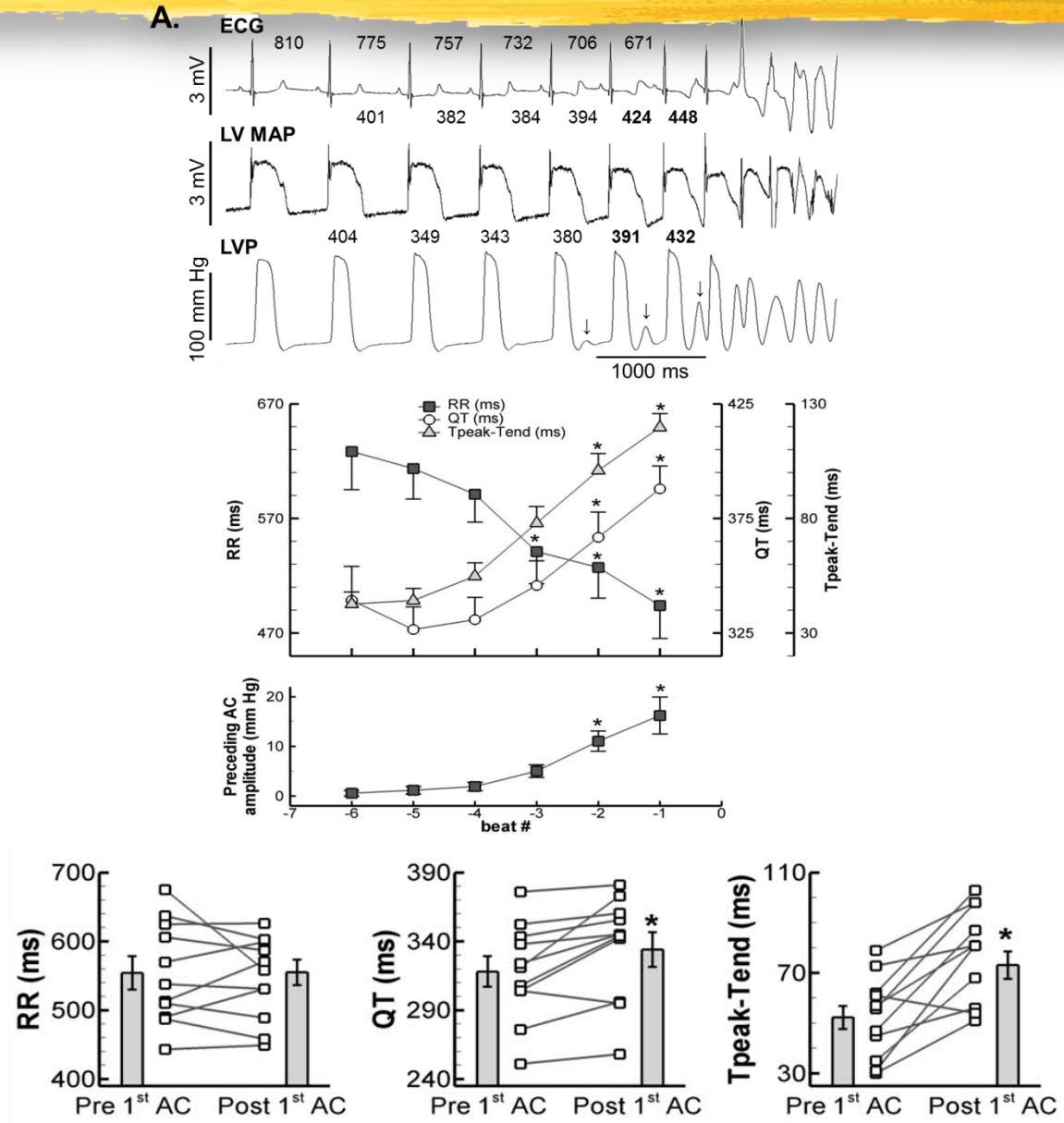
Underlying Mechanisms II



Beyond the Single Cell



Beyond the Single Cell II



Conclusions

- APD prolongation after spontaneous Ca^{2+} release increases BVR.
- I_{Ks} blockade exaggerates this APD prolongation.
- Elimination of spontaneous release via various agents, with and without preserved systolic Ca^{2+} release leads to a decrease in BVR.
- Reduced CICR-dependent inactivation of I_{CaL} after diastolic Ca^{2+} release underlies this AP prolongation.
- These single cell occurrences seem to have an impact in multi-cellular preparations, indicating translational relevance.
- These data provide novel insights into arrhythmogenic mechanisms during Ca^{2+} overload and suggest novel therapeutic antiarrhythmic strategies.

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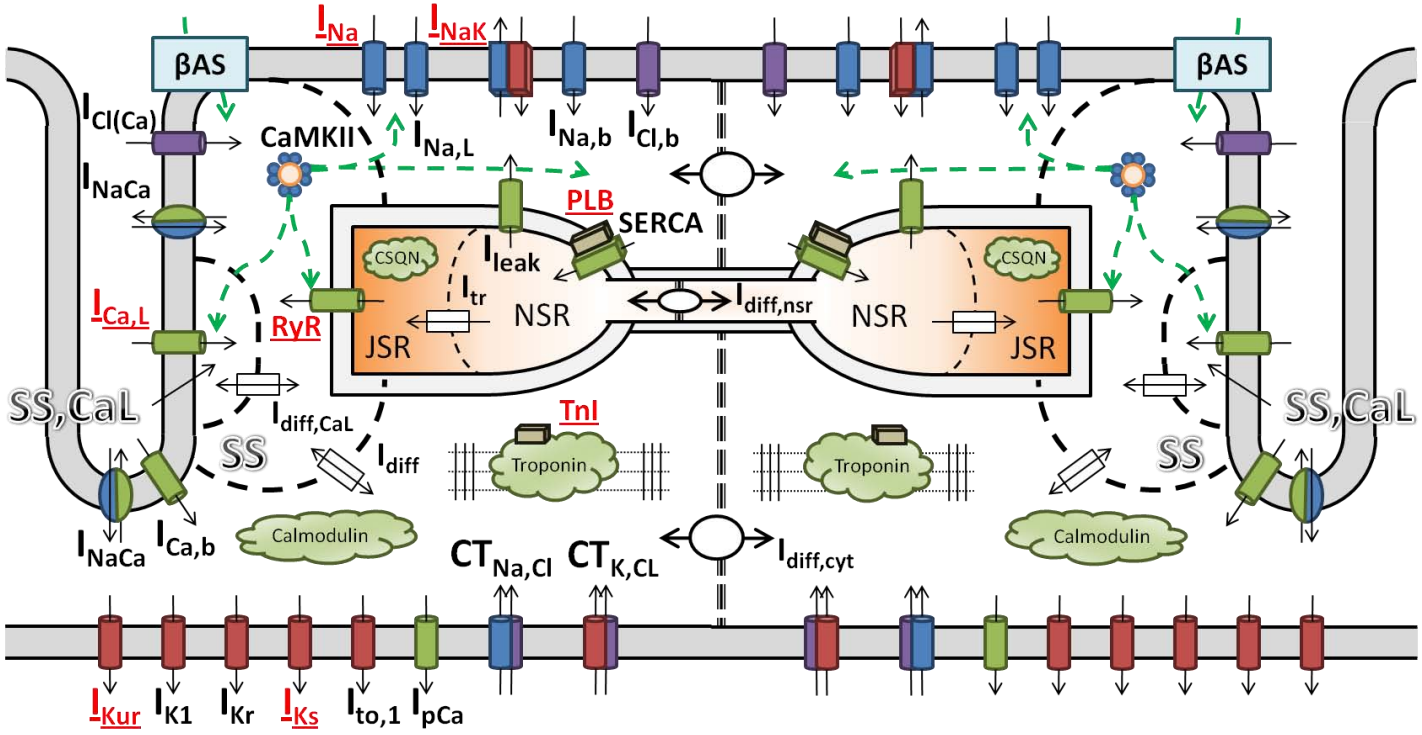
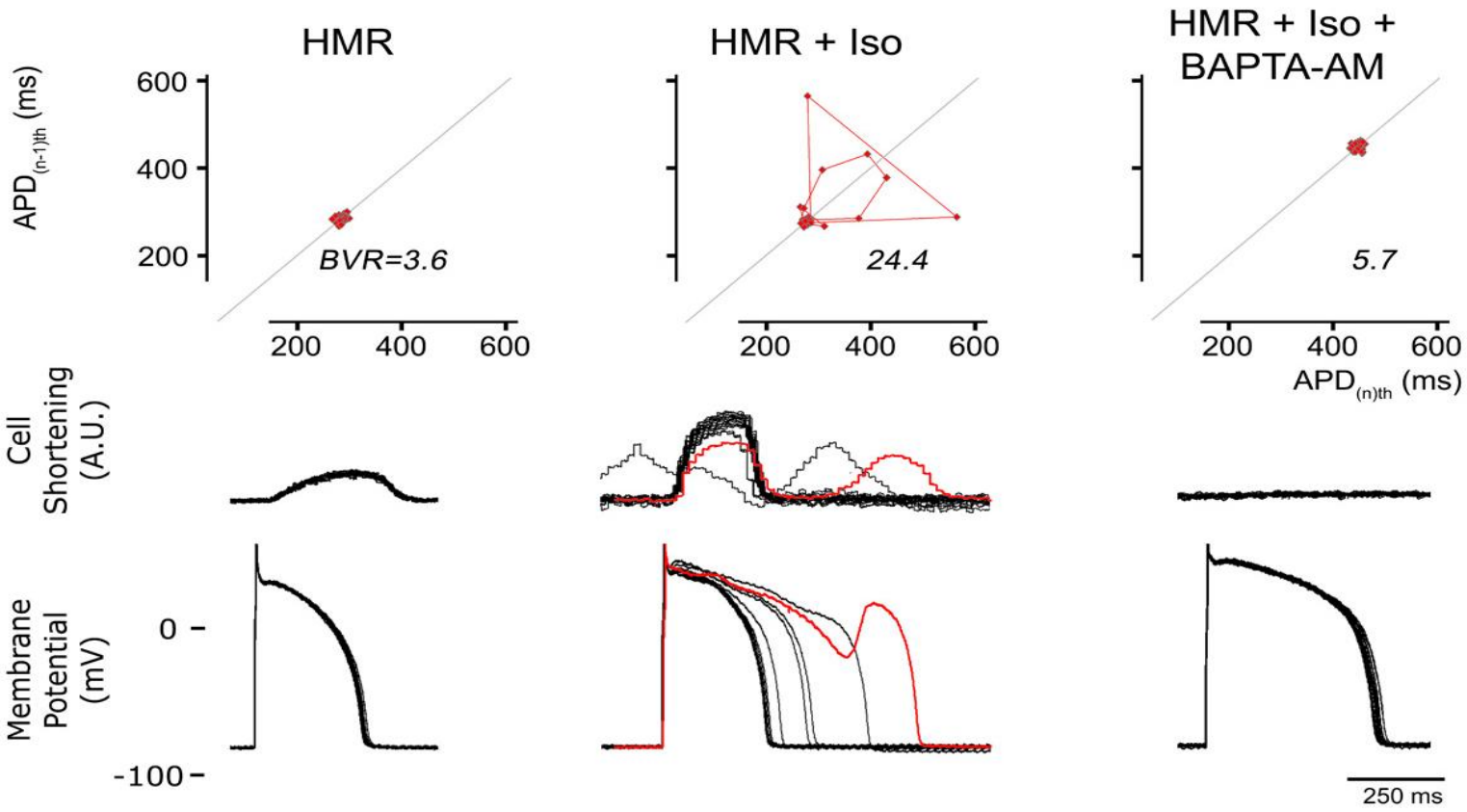
  Henk van der Linde
  David Gallacher

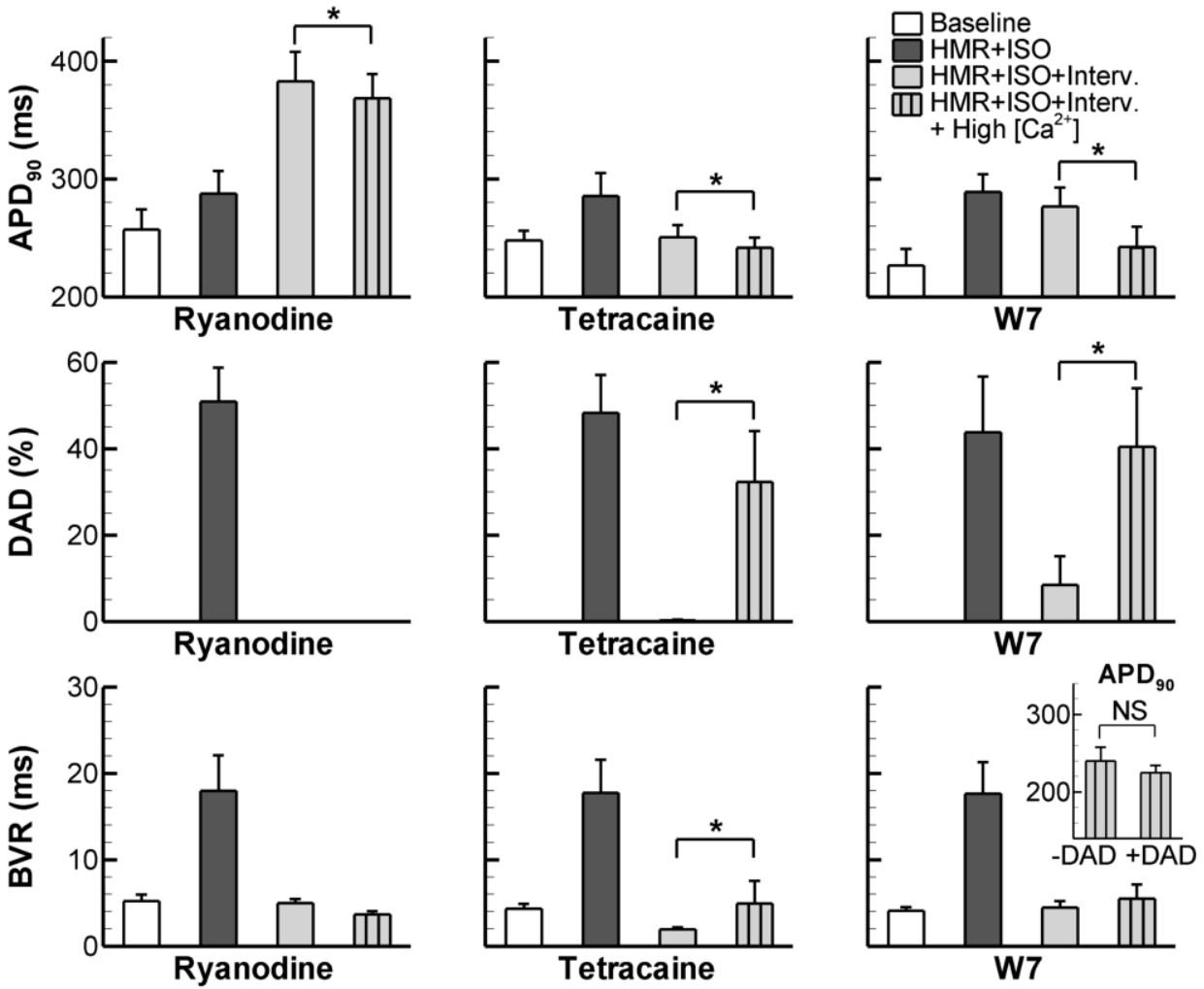
Model Schematic



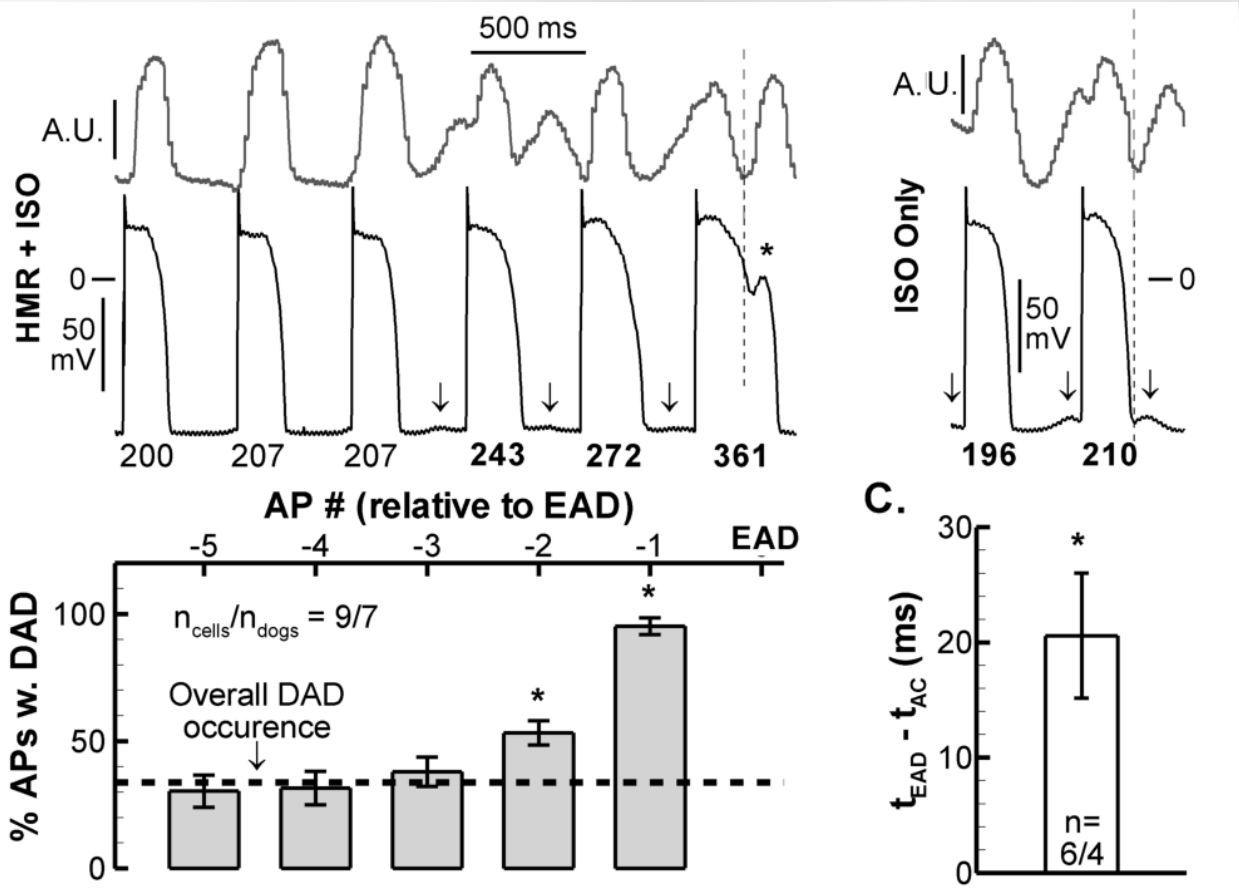
Removing Ca^{2+} Reduced BVR



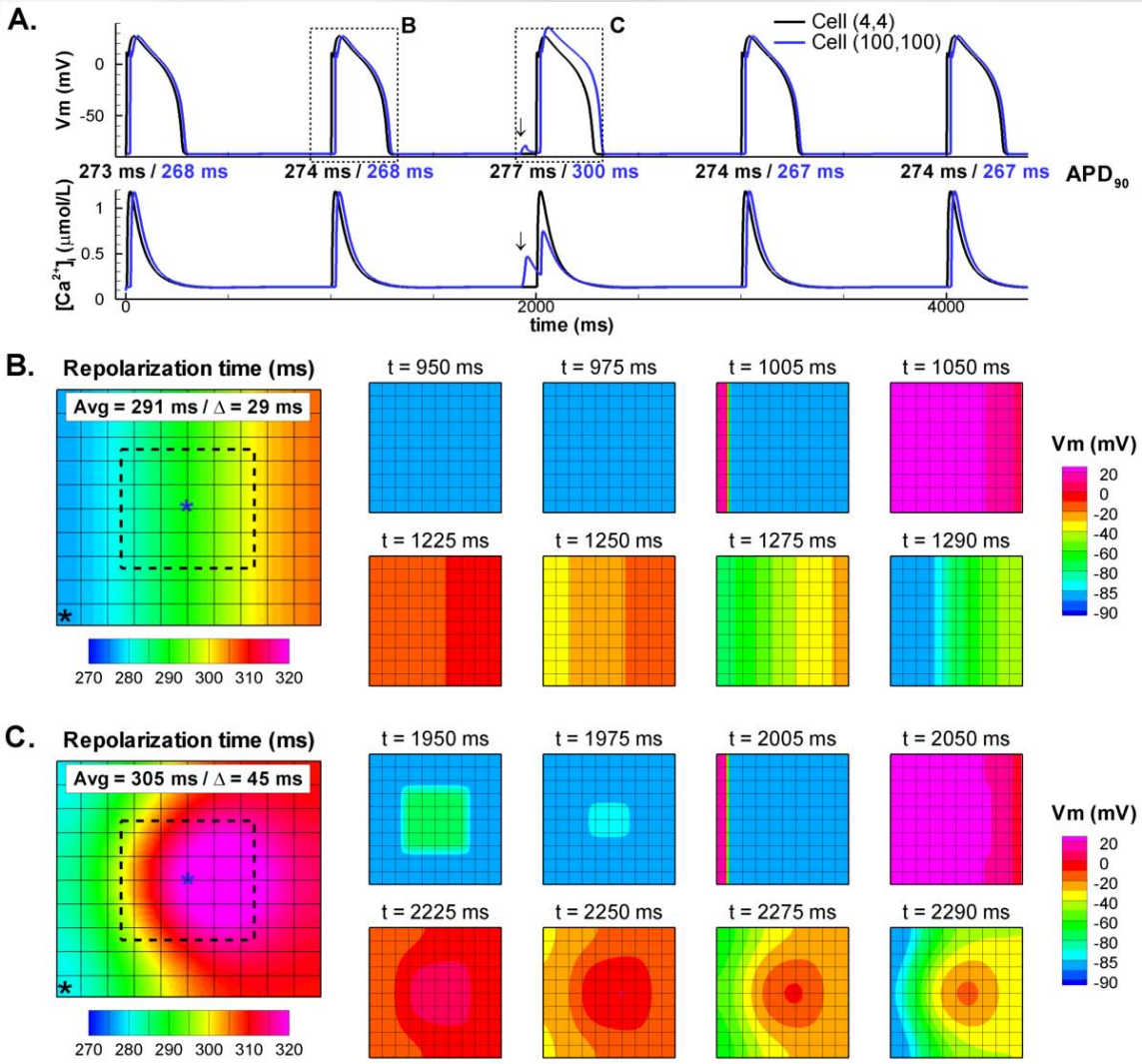
Re-Introduction of DADs



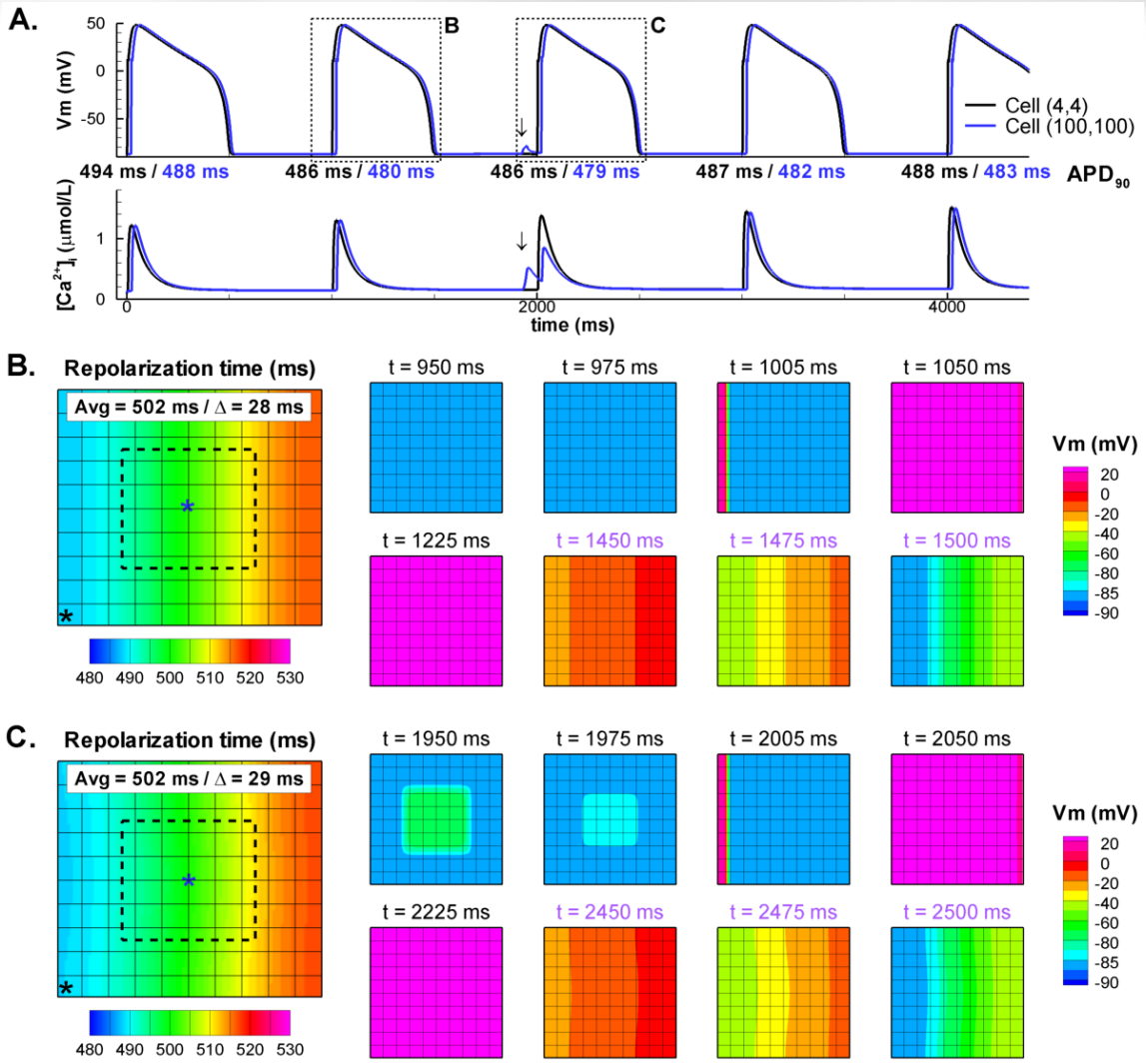
EADs and Spontaneous Calcium Release



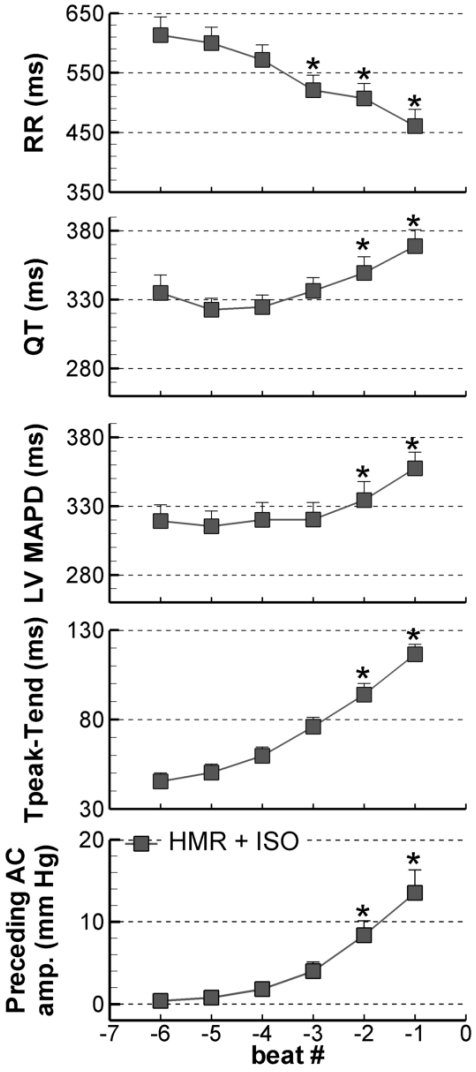
2D Simulations

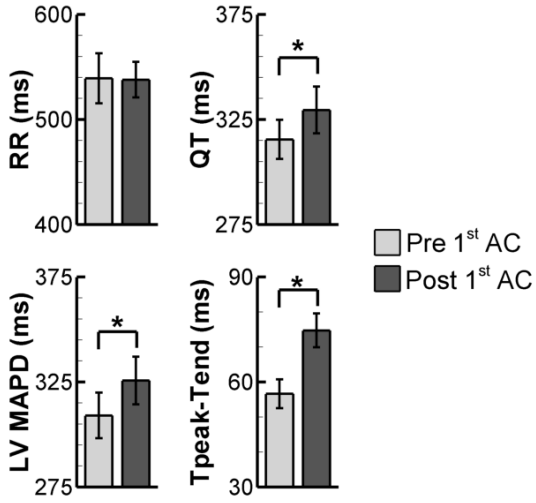


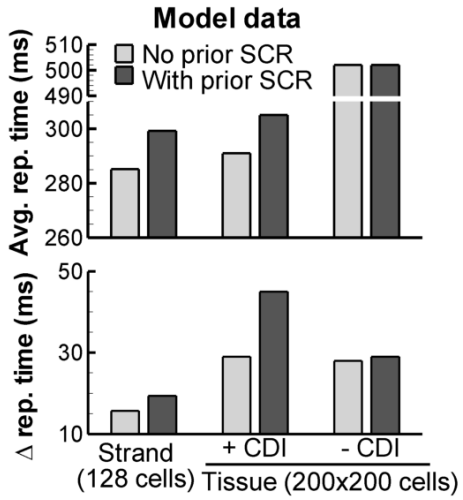
2D Simulations without CDI



In Vivo Summary







In Vivo Summary with Verapamil